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ORIGINAL WORK

Treatment Effect of Early Intravenous Milrinone for Cerebral Vasospasm or Delayed Cerebral Ischemia After Aneurysmal Subarachnoid Hemorrhage

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Abstract

Background: This study assessed the effect of intravenous (IV) milrinone as first-line therapy for cerebral vasospasm (CVS) or delayed cerebral ischemia (DCI) following aneurysmal subarachnoid hemorrhage (aSAH).

Methods: A retrospective study was performed on consecutive patients with aSAH from 2017 to 2022. We assessed the association of IV milrinone treatment with outcomes graded with modified Rankin Scale score at 6 months. We compared the use of alternative therapies for CVS or DCI between patients who received IV milrinone and those who did not. All statistical analyses were performed using STATA 18.0 (StataCorp, College Station, TX).

Results: Of 336 patients, 130 (39%) developed CVS or DCI. Seventy-three patients received IV milrinone and 57 patients did not. Among symptomatic patients, 59% showed improvement in symptoms after milrinone was started. Twenty percent of patients in the milrinone group required vasopressor therapy, whereas 84% of patients were treated with vasopressors in the nonmilrinone group ($p < 0.01$). Thirty one percent of patients receiving milrinone and 56% of patients in the non-milrinone group received endovascular therapy ($p = 0.02$). Univariate analysis showed milrinone was likely associated with good outcome (odds ratio [OR] 2.12 [95% confidence interval [CI] 0.97–4.63]; $p = 0.06$). Propensity score matching analysis confirmed an association between milrinone and good outcome (coefficient 0.30, standard error 0.13 [95% confidence interval [CI] 0.05–0.55]; $p = 0.02$).

Conclusions: Our study showed several potential benefits of early IV milrinone therapy for patients with aSAH with CVS or DCI. Patients who received IV milrinone had better outcome and required vasopressor or endovascular therapy less often. Limitations of the study included several protocol deviations, incomplete documentation of drug effect, and inconsistent assessment of CVS resolution. Early IV milrinone improved outcomes and reduced the use of other therapies to treat CVS and DCI. These results need confirmation in a large clinical trial with stratification of patients by clinical severity, indication, and optimized protocols.

Keywords: Subarachnoid hemorrhage, Intracranial aneurysm, Milrinone, Cerebral vasospasm, Delayed cerebral ischemia

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Introduction

Aneurysmal subarachnoid hemorrhage (aSAH) is a subtype of hemorrhagic stroke that occurs due to rupture of a cerebral aneurysm. After aSAH, patients are at risk for developing cerebral artery vasospasm (CVS) that may lead to ischemic injury. This injury, termed delayed cerebral ischemia (DCI), occurs in approximately 30% of patients with aSAH typically between 3 and 14 days after initial hemorrhage [1]. DCI causes permanent neurological deficits and cognitive impairment leading to significant morbidity and mortality. Therefore, preventing and treating DCI is essential for improving outcome in aSAH survivors.

Given the association of CVS with DCI, different vasodilatory medications have been tested to reduce DCI. To date, only enteral nimodipine has been proven to be effective in decreasing the risk of DCI and improving patient outcome [2, 3]. Commonly used therapies to mitigate the impact of CVS include intravenous (IV) fluids and vasopressors, which are aimed at improving cerebral perfusion. Although these therapies are employed frequently, there have been questions raised about their efficacy as well as reports of serious complications [4–6].

Milrinone is a phosphodiesterase-3 inhibitor that blocks the degradation of intracellular cyclic adenosine monophosphate and cyclic guanosine monophosphate, giving it inotropic, lusitropic, and vasodilatory effects [7]. Several studies have demonstrated that milrinone can improve radiographic vasospasm when given via the intraarterial route [8, 9]. Subsequent studies examining the use of IV milrinone to treat CVS and prevent DCI have shown that it is well-tolerated and associated with decreased rates of DCI and improved outcome [10–12]. Based on this literature, over the last 5 years our institution has increasingly used IV milrinone as first-line therapy for CVS and DCI, often prior to augmenting blood pressure with the initiation of vasopressors. The aim of this study was to evaluate our institutional experience with IV milrinone for CVS or DCI and assess the efficacy of the treatment.

Methods

Patients

Patients aged 18 years or older who were treated for aSAH in the neurosciences intensive care unit (ICU) at a single tertiary hospital between January 1, 2017, and December 31, 2022, were identified from a registry for admitted patients. For patients meeting inclusion criteria, a retrospective chart review was performed to collect the following additional variables: demographics, severity of SAH, presence of hydrocephalus and Glasgow Coma Scale (GCS) at presentation, method of aneurysm treatment, method of CVS or DCI treatment, results of radiologic studies, hospital-acquired complications, and outcomes assessed at follow-up visits with the modified Rankin Scale (mRS). We excluded patients without identifiable aneurysm, those with a ruptured arteriovenous malformation, those who had withdrawal of life-sustaining therapy or death within 3 days after initial bleeding, and those enrolled in other clinical trials for CVS or DCI. This study was approved by the institutional review board.

IV Milrinone Treatment Protocol

The institutional guidelines for the management of CVS or DCI with IV milrinone recommended a bolus of 50 μg/kg followed by an infusion at a rate of 0.5–1.25 μg/kg/min based on the Montreal study [11]. Adjustment of dosing was allowed depending on the severity of CVS or DCI, existing comorbidities, and hemodynamic status. Prespecified reasons for stopping IV milrinone included the development of refractory cardiac arrhythmia, hypotension (recurrent systemic blood pressure < 100 mm Hg despite IV fluid therapy), or high intracranial pressure (ICP) > 20 mm Hg.

When CVS was detected on transcranial doppler (TCD), computed tomography angiography (CTA) or digital subtraction angiography, irrespective of any new neurologic deficit, IV milrinone was initiated and continued until resolution or improvement of CVS was confirmed on follow-up imaging. For patients with new neurologic deficits consistent with DCI, milrinone was also administered immediately. If the observed deficit did not resolve or improve on IV milrinone within 30 min, vasopressors (norepinephrine or phenylephrine) could be added to augment the blood pressure at the treating physician's discretion while maintaining the milrinone infusion until the deficit resolved. If deficits persisted despite milrinone and adequate vasopressor therapy, the endovascular neurosurgery team was consulted for intraarterial therapy with injection of verapamil or angioplasty.

Diagnosis of Cerebral Artery Vasospasm and DCI

We used radiographic and sonographic criteria to diagnose CVS. CTA was performed when new neurological deficits were noted or as a screening tool between postbleed day 5 and 10 if the neurological examination could not be relied on for the detection of cerebral ischemia. CVS was diagnosed on CTA or digital subtraction angiography if cerebral artery caliber was reduced more than 25%. Using TCD, CVS was defined as any of the following: mean flow velocity greater than 120 cm/s in the intracranial internal carotid artery,

anterior cerebral artery, or middle cerebral artery or greater than 50 cm/s in the basilar artery; increase in mean flow velocity of more than 50% in a 24-h period; or a Lindegaard ratio greater than 3.0. DCI was diagnosed when physicians noted any new neurological deficits referrable to a vascular territory not explained by other causes such as worsening hydrocephalus, cerebral edema, fever, or seizure.

Statistical Analysis

The primary objective of the study was to assess the association of outcomes with IV milrinone treatment for CVS or DCI after aSAH. The second aim was to compare the use of alternative therapies for CVS or DCI between patients who received IV milrinone and those who did not. First, we compared clinical factors among patients with CVS or DCI who received IV milrinone with those of patients who did not in order to identify any determinants of the treatment decision that may have affected outcomes. Second, we conducted univariate analysis on the associations of clinically relevant factors with outcomes. We defined mRS 0–2 at 6-month follow-up as a good outcome and mRS > 2 as a poor outcome. mRS was documented during postdischarge visits to a neurosurgery clinic by clinicians who were not involved in ICU management. For patients whose mRS was not explicitly documented in the electronic health record, study staff (HYB) inferred mRS after reviewing the interviews with patients or their caregivers. We performed a *t*-test for continuous variables or Pearson's χ^2 test for categorical variables to compare the characteristics of each patient group. Subsequently, we selected variables with the cutoff value $p < 0.10$ in the univariable analysis and conducted a multivariable logistic regression using stepwise regression. We performed the likelihood ratio test and checked multicolinearity. To reduce selection bias, a subsequent analysis using propensity score matching was performed to measure the average treatment effect on the treated (ATT). A priori, we selected variables for propensity matching we believed were associated with both outcome and treatment allocation. Propensity scores were calculated using logistic regression. Matching of propensity scores was conducted using nearest neighbor matching with a ratio of 1:1 and caliper 0.2. The matching was examined for quality and adjusted to achieve a good balance of propensity scores and minimize the standardized mean difference of each covariate. We tested different matching algorithms and perform sensitivity analysis in order to determine the optimal model. High-grade Hunt and Hess (HH) score and GCS at presentation had a correlation. HH score had a significant effect on outcome but was only weakly related to treatment assignment. When HH score was introduced into the model, the effect of treatment with milrinone did not change significantly but a balance of covariates could not be achieved. The variables that were included in the final model were age, presence of intracerebral hemorrhage or hydrocephalus, modified Fisher score, and cardiac disease. All statistical analyses were performed using STATA 18.0 (StataCorp, College Station, TX).

Results

Three hundred and thirty-six patients met the inclusion criteria. Of those, 130 patients developed CVS or DCI (39%): 80 patients had DCI with CVS, 8 had DCI without CVS, and 42 had CVS without DCI. Among the 42 patients with CVS without DCI, 26 patients had reliable neurological examination with good mentation, but 16 patients could not be adequately assessed due to a depressed level of consciousness for various reasons such as high-grade aSAH (Fig. 1).

Patient Characteristics

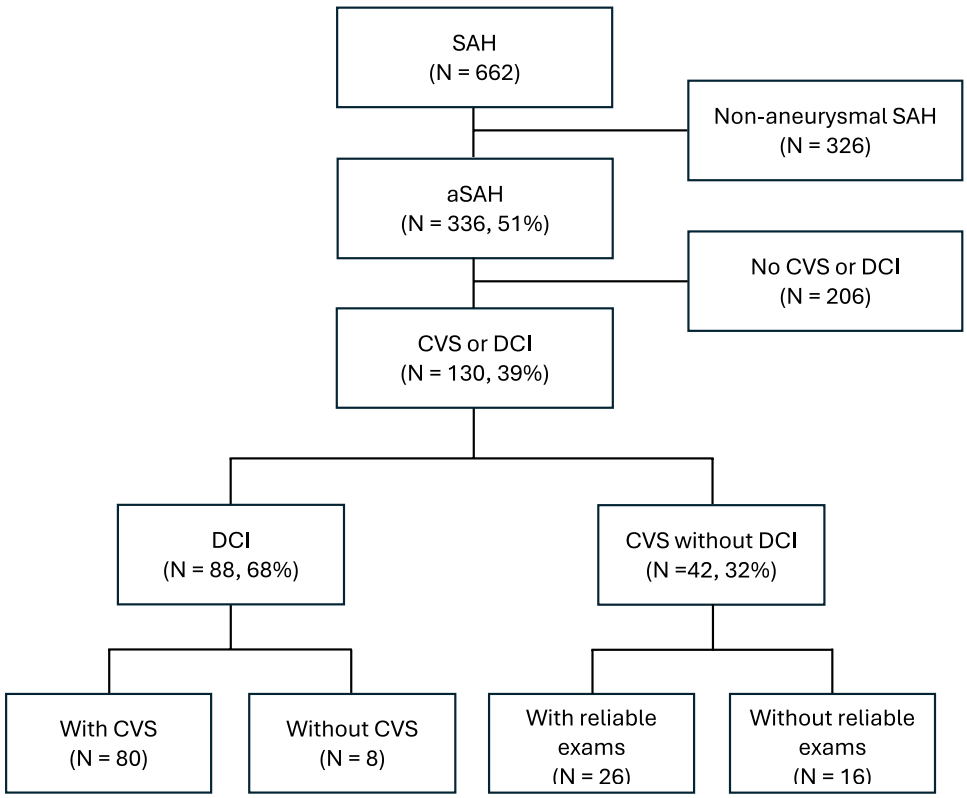
The mean age of 130 patients who developed CVS or DCI was 57 ± 13 years old. Sixty-seven percent of the patients were female. Among all patients, 73 patients (56%) were treated with IV milrinone for CVS or DCI at least once during the hospitalization, and 57 patients never received milrinone. Overall, patient characteristics were similar between the IV milrinone and nonmilrinone groups (Table 1).

IV Milrinone Treatment

Thirteen patients (18%) did not receive a bolus prior to the infusion. For patients who received a bolus, the dose ranged from 25 μg/kg to 100 μg/kg. The initial infusion rate varied between 0.25 and 0.75 μg/kg/min and was increased up to 1.25 μg/kg/min if symptoms persisted. Because of recurrent CVS or DCI, 14 patients (19%) had IV milrinone restarted after the initial infusion had been completed. In eight patients (seven patients for DCI and one patient for CVS without DCI), IV milrinone was stopped after less than 6 h for various reasons before CVS or neurological deficits improved (see Supplementary Table 1). Patients with DCI receiving milrinone for less than 6 h were excluded, and 49 of 81 patients with DCI (60%) received milrinone for an average of 7 ± 5 days.

Efficacy of IV Milrinone Treatment for DCI

Among the 49 patients with DCI who received milrinone, symptomatic improvement was documented in 29 patients (59%) before the rate of the infusion was increased or other therapies were started. Ten of 49 patients (20%) in the milrinone group subsequently



aSAH, aneurysmal subarachnoid hemorrhage; CVS, cerebral artery vasospasm; DCI, delayed cerebral ischemia.

Fig. 1 Classification of patients. aSAH, aneurysmal subarachnoid hemorrhage, CVS, cerebral artery vasospasm, DCI, delayed cerebral ischemia, SAH, subarachnoid hemorrhage

Table 1 Comparison of the characteristics between the milrinone and nonmilrinone groups at the time when treatment for CVS or DCI was initiated

Characteristics	CVS or DCI ($n=130$)	Milrinone ($n=73$, 56%)	Nonmilrinone ($n=57$, 44%)	p value
Age, mean (SD)	57 (13)	56 (13)	58(13)	0.47
Female, *n* (%)	87 (67)	47 (64)	40 (70)	0.49
HH 4–5, *n* (%)	49 (38)	26 (36)	23 (40)	0.58
mFS 3–4, *n* (%)	117 (90)	68 (93)	49 (86)	0.29
GCS, mean (SD)	11 (5)	11 (5)	11 (5)	0.87
Endovascular therapy, *n* (%)	105 (81)	61 (85)	44 (76)	0.36
Hydrocephalus, *n* (%)	105 (81)	60 (83)	45(79)	0.64
Coexistent ICH, *n* (%)	24 (18)	15 (21)	9 (16)	0.49
Noninfectious fever, *n* (%)	42 (32)	23 (32)	19 (33)	0.83

CVS, cerebral artery vasospasm, DCI, delayed cerebral ischemia, GCS, Glasgow Coma Scale, HH, Hunt and Hess scale, ICH, intracerebral hemorrhage, mFS, modified Fisher Score, SD, standard deviation

required vasopressor therapy, whereas 27 of 32 patients (84%) were treated with vasopressors in the nonmilrinone group ($p<0.01$). In patients with DCI receiving milrinone, 15 of 49 patients (31%) underwent endovascular therapy compared with 18 of 32 patients (56%) in the nonmilrinone group ($p=0.02$) (Table 2).

Association of IV Milrinone Treatment with Outcomes

Of 130 patients who developed CVS or DCI, 107 patients were available for 6-month outcome assessment. Eight patients who received milrinone for less than 6 h were excluded. Six patients in the IV milrinone group and nine in the nonmilrinone group were lost to follow-up. Of these 107 patients, 59 patients (55%) received IV milrinone until CVS or DCI was resolved and 48 patients (45%) never received milrinone. Patients who received milrinone and those who did not had similar baseline clinical characteristics (Supplementary Table 2). Patients treated with milrinone trended toward better outcome (mRS 0–2) (66% vs. 48%, $p=0.058$; Fig. 2).

A univariable logistic analysis showed a possible association of IV milrinone with good outcome (odds ratio [OR] 2.12, 95% confidence interval [CI] 0.97–4.63; $p=0.06$) whereas age, HH score 4–5, presence of hydrocephalus, low GCS, and intracerebral hemorrhage were associated with poor outcome (Supplementary Table 3).

In a multivariable analysis, age was associated with poor outcome (adjusted OR [aOR] 0.94, 95% CI 0.90–0.99; $p<0.01$). High-grade HH score tended to be negatively associated with good outcome (aOR 0.25, 95% CI 0.06–1.05; $p=0.06$) whereas IV milrinone use demonstrated a weak trend toward good outcome (aOR 2.46, 95% CI 0.90–6.71; $p=0.08$) (Table 3). In the propensity score matching including age, presence of intracerebral hemorrhage or hydrocephalus, modified Fisher score and cardiac disease, patients who received IV milrinone were 30% more likely to have good outcome (coefficient 0.30, 95% CI 0.05–0.55; $p=0.02$) (see Supplementary Fig. 1).

Hemodynamic Changes and Cerebral Perfusion Pressure

Among patients receiving milrinone, the average systolic blood pressure (SBP) immediately preceding the treatment was 157 ± 27 mm Hg. The SBP within 1 h of starting therapy was 152 ± 28 mm Hg. The median change in heart rate 1 h after the initation of IV milrinone was 8 bpm (interquartile range [IQR] 1–16) (see Supplementary Fig. 2). Adverse hemodynamic events occurred in 7 of 73 patients (10%) who received IV milrinone. Two patients experienced hypotension (SBP < 100 mm Hg), and five patients experienced arrhythmia (new premature atrial contraction in one patient, rapid ventricular response in two patients with preexisting atrial fibrillation, and sinus tachycardia with heart rate greater than 140 bpm in two patients).

Fifty-nine of 73 patients (81%) in the milrinone group had an ICP monitoring device at the time they received the treatment. The median value of the highest ICP experienced during treatment was 10 mm Hg (IQR 3–15 mm Hg). While receiving milrinone, five patients (8%) had at least one episode of persistently elevated ICP > 20 mm Hg. All of these patients had intermittently elevated ICP

Table 2 Comparison of vasopressor use and endovascular treatment for DCI between the milrinone and nonmilrinone groups

Patients with DCI ($n=81$)	Vasopressor	Endovascular therapy
Milrinone ($n=49$), *n* (%)[a]	10 (20)	15 (31)
Nonmilrinone ($n=32$), *n* (%)	27 (84)	18 (56)
p value	< 0.01	0.02

DCI, delayed cerebral ischemia

[a] For the milrinone group, only vasopressor use and endovascular therapy that were required after the initiation of intravenous milrinone were counted

Table 3 Multivariable logistic regression to investigate the association of clinical factors with good outcome

Clinical factors	aOR	95% CI	*p* value
Age	0.94	0.90–0.99	< 0.01
HH 4–5	0.25	0.06–1.05	0.06
Hydrocephalus	0.90	0.24–3.30	0.87
GCS	1.11	0.94–1.31	0.22
ICH	0.34	0.09–1.32	0.12
IV milrinone	2.46	0.90–6.71	0.08

aOR, adjusted odds ratio, CI, confidence interval, GCS, Glasgow Coma Scale, HH, Hunt and Hess scale, ICH, intracerebral hemorrhage

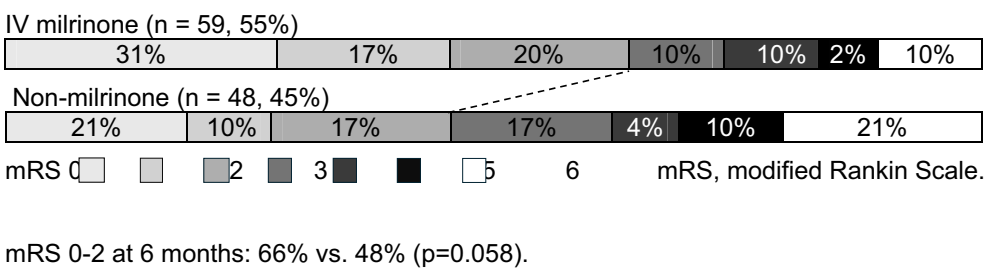


Fig. 2 Comparison of mRS between the milrinone and nonmilrinone groups at the 6-month follow-up. IV, intravenous, mRS, modified Rankin Scale

prior to receiving treatment. Prior to starting milrinone, the median cerebral perfusion pressure was 102 mm Hg (IQR 94–116 mm Hg) and 60 min after starting milrinone it was 105 mm Hg (IQR 95–119 mm Hg).

Discussion

This study demonstrated several potential benefits of early IV milrinone therapy for patients with aSAH with CVS or DCI. In a propensity matched analysis, IV milrinone was associated with improved outcome. Additionally, patients with DCI who received IV milrinone required vasopressor or endovascular therapy less often than those who did not receive milrinone. Among symptomatic patients who received milrinone for DCI, more than half showed improvement in their neurologic deficit before the dose was increased or additional therapies were started. Finally, IV milrinone treatment carried low risk of adverse effects.

In the MILRISPASM study, rates of endovascular therapy in patients receiving milrinone were reported to be 15%, which compares favorably with the 31% of patients who received endovascular treatment while on milrinone in this study [12]. Possible explanations for this variation include differences in the severity of vasospasm between study populations, a higher threshold to initiate endovascular therapy in the MILRISPASM cohort, or a beneficial effect of using milrinone in combination with a higher mean arterial pressure (MAP) goal. Although our study used milrinone doses in a range between 0.25 and 1.25 μg/kg/min, another recent study using a higher rate of milrinone up to 2.5 μg/kg/min reported that only 19% of patients required endovascular treatment [13]. This may imply that a higher dosage of milrinone is required to maximize the potential benefit of the therapy. Although the study by Lannes et al. [11] did not include a comparison group, 65% of patients receiving milrinone in their study had a good functional outcome (mRS 0–2) within 12 months. The MILRISPASM study also showed better outcome in the treatment group versus controls (76% vs. 55%) [12].

The use of IV milrinone in our study has several notable features when compared with previous reports using the same medication after aSAH. In a disease process in which cerebral ischemia is thought to be exacerbated by vasoconstriction, it is intuitively appealing to avoid vasopressors that may further reduce vessel caliber, if possible [14, 15]. In the MILRISPASM study, vasopressors were initiated as first-line treatment to target a MAP of 100–120 mm Hg and milrinone was started 1 h afterward so long as MAP goals were maintained [12]. In addition, using a vasopressor prior to milrinone may attenuate any beneficial impact of the latter, or higher doses of milrinone may be needed to have the same effect. We chose to manage CVS or DCI by using the neurologic examination as the best indicator of adequate cerebral perfusion. In patients who demonstrate radiographic CVS *without* clinical deterioration, our protocol is to initiate milrinone without augmenting blood pressure with vasopressors. Patients with a normal neurologic examination are unlikely to benefit substantially from increasing cerebral perfusion pressure so long as the examination remains unchanged, and the introduction of exogenous catecholamines has the risk of worsening CVS in addition to deleterious cardiac and renal effects [16–18]. At the first sign of cerebral ischemia, a bolus of milrinone was given followed by an infusion, reasoning that cerebral vasodilation and increased cardiac output would improve cerebral blood flow without necessarily requiring augmentation of blood pressure. As long as the neurologic examination had returned to baseline or was rapidly improving, a blood pressure target lower than that used in the MILRISPASM study [12] was tolerated. After clinical observation for at least 30 min, if milrinone had not extinguished the neurologic deficit, vasopressors were added in a stepwise fashion to raise the blood pressure. Given that the role of milrinone in augmenting cerebral blood flow in the setting of CVS has not been rigorously established, we felt that a period of 30 min was a reasonable, but ultimately arbitrary time period to wait for a clinical response to milrinone before initiating vasopressors. Although a longer period could have been used to observe a clinical improvement with milrinone by itself, we believed this would increase risk of leaving ischemia undertreated. We reasoned that if milrinone had not reversed the neurologic deterioration promptly, additional augmentation of cerebral perfusion pressure would be needed to restore adequate perfusion. It is possible that a longer period of observation prior to the initiation of pressors would have resulted in greater degrees of improvement on milrinone alone and a lower rate of vasopressor usage in the treatment group. Conversely, for patients in whom milrinone did not restore adequate cerebral perfusion, a delay to blood pressure augmentation could have increased risk. In the setting of symptomatic CVS, it is impossible to ascertain which mechanism of therapy will have a more salutary effect on cerebral blood flow; a drug that vasodilates cerebral arterioles and is relatively blood pressure neutral, or a drug that raises systemic blood pressure while also potentially constricting cerebral arteries further [14, 15, 19]. If milrinone improves outcomes through a mechanism different than vasodilation of cerebral blood vessels such as anti-inflammatory or antithrombotic effects [20–22], the sequence of its initiation relative

to that of catecholamine vasopressors may not matter. However, if vasodilation is the primary protective pathway, some patients may be adequately treated with milrinone alone. Furthermore, a decreased risk of complications of vasopressor use may contribute to better outcome. This potential benefit of IV milrinone prior to vasopressor use and the underlying mechanism needs to be studied with a larger sample.

Our study has several limitations, many of which are related to its retrospective nature. Protocol deviations occurred during the study period such that in some patients milrinone was started at virtually the same time as vasopressors or at the time of endovascular therapy hindering the evaluation of the effects of milrinone alone. Documentation of the clinical effect of milrinone was incomplete in some instances. During the study period, TCD availability was limited without a dedicated technician. Therefore, we did not consistently assess the effect of milrinone on CVS before and after the medication was started, which might have helped elucidate the mechanism of its beneficial effect. Given the small sample size, patients who were lost to follow-up and not included in the outcome analysis might have affected the results significantly.

Of most significant concern is accounting for why some patients received milrinone while others did not. The use of milrinone was adopted as a quality improvement project that was agreed on by neurointensivists and neurosurgeons. The use of the protocol was recommended but was ultimately at the treating physician's discretion. At the time, the protocol was launched there were different levels of comfort using milrinone among the various ICU providers. Some of the neurocritical care faculty were more enthusiastic about ensuring that all eligible patients were started on the medications while others were less so. Early in the roll-out of the protocol, ICU providers who were less familiar with milrinone did not always administer the drug immediately when patients developed the appropriate criteria. Over the next 2 years adoption of the protocol became more uniform across different team members and most eligible patients received milrinone in a timely fashion. Although the propensity score matching analysis showed that there was an association between milrinone treatment and good outcome, it is still possible that additional unknown factors or excluded variables could have affected the use of milrinone or outcome that if included would have changed our results. This is more likely in light of a small sample size and a relatively large number of variables.

Conclusions

The present study demonstrated that IV milrinone as a first-line therapy for CVS or DCI after aSAH improved outcomes, reduced use of vasopressor and endovascular therapies, and was safe. These beneficial effects of IV milrinone need confirmation in a large randomized controlled trial with stratification of patients by clinical severity and indication. Our study raises questions about the optimal timing for initiation of IV milrinone and the sequence in which therapies to mitigate the impact of DCI are employed. Currently, an ongoing randomized controlled trial Milrinone Infusion for VAsospasm treatment in subarachnoid hemoRrhage (MIVAR) is studying the effects of milrinone on CVS and DCI as add-on therapy following blood pressure augmentation. Given the possible antagonistic mechanisms of action of milrinone and vasopressors, additional studies are needed to explore whether milrinone should be employed as first-line therapy in all cases.

Supplementary Information
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Author Contributions
Hae-Young Baang designed the study, acquired and analyzed data, and drafted the article and revised it critically. Alexandra S. Reynolds contributed to design of the study and revised the article critically. Neha Dangayach contributed to design of the study. Emily J. Gilmore contributed to design of the study and revised the article critically. Jennifer A. Kim contributed to design of the study and revised the article critically. Cappi Lay formulated the idea and design of the study, analyzed data, drafted the article, and revised it critically for important intellectual content. All authors approved the final version of the article for publication and agreed to be accountable for all aspects of the work ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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Conflicts of interest
None.

Ethical Approval/Informed Consent
This retrospective study was approved by the institutional review board and followed ethical guidelines strictly.

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